RAUWILOID IN HYPERTENSION

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Although *Rauwolfia serpentina* has been widely used in India for many years, it is only since Vakil's paper in 1949[1] that this drug has aroused pharmacological interest and has come into general medical use in the treatment of hypertension. During the few years that have elapsed since the first report on this subject a large volume of literature has accumulated and a number of different preparations have become available for the treatment of hypertension.

These preparations can be divided into 3 groups as follows: (1) Whole-root preparations (Serpina, Preparation 1043, Raudixin), (2) pure alkaloids (reserpine, rescinnamine), and (3) 'Alkaloidal extracts (Roxinil, Rauwiloid).

1. *Whole-root preparations* consist of powdered dried root. 'Serpina' is a preparation which was originally used in India, and was reported on in the earlier American communications.[1-2] Preparation 1043 (Riker) and Raudixin (Squibb) next became available.[3] Raudixin is still in common use where administration of a whole-root preparation is desired.

2. *Pure alkaloids.* The hypotensive action of *Rauwolfia serpentina* is due to its alkaloids, of which so far about 15 have been isolated.[4] Only 2 alkaloids that have been used in the pure form are so far available to the profession, viz. reserpine (Serpasil, Ciba) and rescinnamine (Riker).

3. *'Alkaloidal' extracts.* There is some evidence that other alkaloids apart from reserpine and rescinnamine exert a hypotensive action, and 2 alkaloidal extracts have become available, namely Roxinil (Merck) and Rauwiloid (Riker). Roxinil contains a number of alkaloids of reserpine-like action and a serpentine-like material. Rauwiloid is an extract of the alseroxylon fraction of the alkaloids, consisting of reserpine and rescinnamine, which provide about 60% of the activity, and other, as yet unidentified active alkaloids.

PHARMACOLOGICAL ASPECTS

Most of the detailed work on the action of *Rauwolfia serpentina* has been done with the pure alkaloid reserpine. It is now well established that it has a sedative and tranquillizing action on the central nervous system, which is quite different from the sedation produced by barbiturates. In addition it stimulates the reticular formation of the medulla of certain animals. Rinaldi and Himwich[5] have suggested that this action is the basis of the parkinsonian-like tremor which is sometimes produced in man. Reserpine has also been shown to lower the threshold for convulsive seizures,[6] thus increasing the frequency of fits in epileptics[7] and to be antagonistic to phenytoin.[8]

Although it has been widely used, and in large doses, in mental hospitals for its tranquillizing effect, reserpine can cause severe depression, agitation and psychosis in hypertensive patients on long-term treatment.

There is ample evidence to suggest that the blood-pressure-lowering effect of reserpine is of central origin. However, it is obvious that any hypotensive drug must produce its ultimate effect either by diminishing the force of cardiac contraction and cardiac output or by reducing the peripheral resistance. In dogs, cardiac output is not decreased to any significant extent after the administration of reserpine[9] and the fall in blood pressure is due to a decrease in the peripheral resistance.

Reserpine appears to produce its effect by damping down the afferent impulses reaching the medulla and thus reflexly diminishing the central sympathetic outflow.[10] It is well established that inhibition of central vasoconstrictor impulses can effectively reduce peripheral resistance and cause lowering of the blood pressure. Depression of sympathetic activity leads to overaction of the parasympathetic nervous system, thus producing myosis, bradycardia and diarrhoea, which was first observed by Bein[11] to occur after the administration of reserpine.

AUTHORS' INVESTIGATIONS

A. ACUTE EXPERIMENTS

The effect of intravenous injection of reserpine on blood pressure and peripheral blood flow.

Reserpine* was given by single or repeated intravenous injection to 10 patients, 2 of whom had severe hypertension, 2 were cases of mild hypertension, 4 had a recurrence of hypertension after a lumbo-dorsal splanchnicectomy (Smithwick operation), 1 had had all four limbs sympathectomized for Raynaud's disease, and 1 had had a unilateral lumbar sympathectomy for varicose ulceration. Continuous records were obtained of the peripheral circulation by means of the optical digital plethysmograph described in detail elsewhere.[12-14] This sensitive method not only allows correct registration of the height of the pulse volume of two digits simultaneously, but also permits calculation of the arterial inflow by means of the venous-congestion test. The blood pressure was taken at regular intervals by clinical methods and the heart rate was, of course, available from the plethysmographic records. Only those 'Smithwick' patients were selected in whom the operation had included removal of the first and second lumbar ganglia, i.e. the lower limbs had been sympathectomized. All were examined for sympathetic activity in the lower extremities to ascertain that the sympathectomy was complete. As at Groote Schuur Hospital, at one time, sympathectomy had been extended to include the thoracic chain up to D_2,[15] the hands were examined as well to ascertain whether the vessels of the hands were under full sympathetic control.

Fig. 1. demonstrates such a preliminary test in the patient whose response to reserpine is shown in Fig. 4. After body heating by immersion of one upper limb in water at 45°C there is marked reflex vasodilatation of the other upper limb, due to the release of sympathetic tone. In the lower (sympathectomized) extremities, however, a decrease in pulse volume is recorded.

As has previously been demonstrated[12] this is typical of a sympathectomized limb and is due to shunting of blood away from the sympathectomized limb to other vascular beds which respond with reflex dilatation. The sympathectomized vessels respond to local heating with dilatation, indicating that the failure to respond to reflex heating was not due to organic changes. In addition, absence of thermoregulatory sweating was observed in the lower limbs of all 'Smithwick' patients. Similar tests were carried out in the patient who had had all four limbs sympathectomized for Raynaud's disease and in the patient who had had a unilateral lumbar sympathectomy. They showed conclusively that

* We gratefully acknowledge the supply of 'Serpiloid', a pure reserpine preparation, by Riker Laboratories, Port Elizabeth.

TABLE I. EFFECT ON BLOOD PRESSURE AND PULSE VOLUME OF INTRAVENOUS INJECTION OF RESERPINE

Patient	*Average Resting Blood Pressure*	*Dose*	*How given intravenously*	*Average Final Blood Pressure*	*Fall in Blood Pressure*	*Pulse Volume*		*Remarks*
						Normal Digit	*Sympathectomized Digit*	
1	225/118	1·5 mg.	1 dose	230/105	25/13	Finger: gradual dilatation Toe: gradual dilatation		The gradual increase in pulse volume observed in these cases is commonly seen on prolonged rest and is due to release of sympathetic tone.
2	230/128	2 mg.	1 dose	206/118	24/10	Finger: slight dilatation Toe: gradual dilatation		
3	172/126	4 mg.	4×1 mg.	154/100	22/26	Finger: slight dilatation Toe: gradual dilatation		
4	172/88	2·5 mg.	2×1 mg. 1×0·5 mg.	164/80	8/8	Finger: unchanged Toe: gradual dilatation		
5	245/145	1·5 mg.	1 dose	110/80	135/65	Finger: slight dilatation	Toe: marked fairly rapid dilation	Previous Smithwick operation
6	230/155	2 mg.	2×1 mg.	160/122	70/33	Finger: constriction	Toe: marked fairly rapid dilatation	Previous Smithwick operation
7	230/124	3 mg.	3×1 mg.	112/74	118/50	Finger: slight dilatation	Toe: marked rapid dilatation	Previous Smithwick operation
8	245/150	1 mg.	1 dose	228/128	17/22	Finger: gradual dilatation	Toe: gradual dilatation	Previous Smithwick operation. Fall in blood pressure very slight; possibly due to small dose of reserpine administered
9	142/74	2 mg.	1 dose	116/63	22/11		Finger: marked very rapid dilatation Toe: marked very rapid dilatation	All four limbs sympathectomized for Raynaud's disease
10	118/76	2 mg.	1 dose	110/64	8/12	Right toe: Unchanged	Left toe: marked dilatation	Unilateral lumbar sympathectomy for varicose ulcer

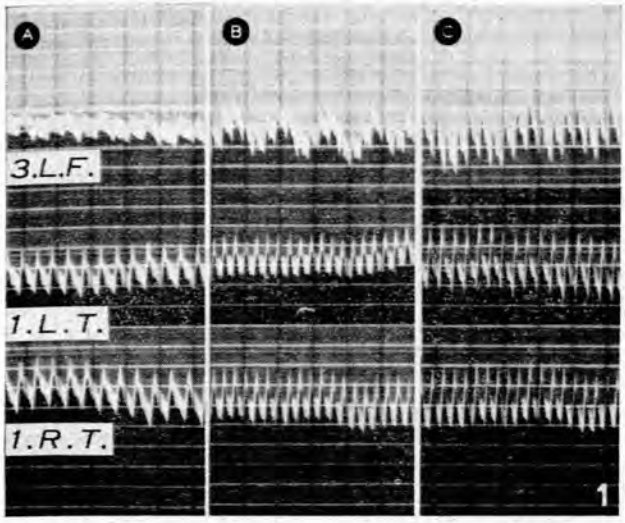

Fig. 1. Pulse volume of the third left finger (3.L.F.), first left toe (1.L.T.) and first right toe (1.R.T.) in a patient who had previously undergone a lumbo-dorsal splanchnicectomy for hypertension.
A. Before body heating. B. After body heating. Note the increase in pulse volume of the finger and the decrease in the toes, demonstrating that the vessels of the finger are under normal sympathetic tone, whereas those of the toes are sympathectomized. C. Response to local application of heat. Note particularly the increase in the pulse volume of the toes indicating that the failure to respond to body heating was not due to organic arterial disease of the vessels.

the sympathectomies were complete and that there was no organic vascular occlusion.

Results

The results are summarized in Table I. They differed both as regards peripheral vascular and hypotensive effect, according to whether the sympathetic vasomotor supply was 'normal' or had been interrupted. Whereas the intravenous

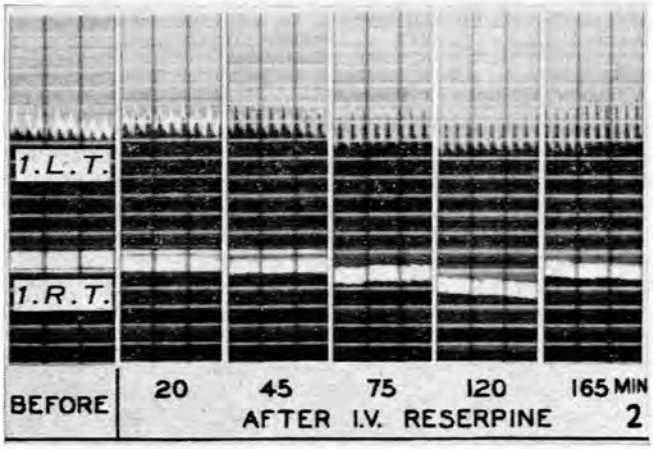

Fig. 2. Effect of 2 mg. of intravenous reserpine on blood flow of first left toe (1.L.T.) and first right toe (1.R.T.) in a patient who has had a left lumbar sympathectomy for varicose ulcers. Tracings recorded before and after injection at times indicated. Note the marked vasodilatation of the sympathectomized vessels (1.L.T.), whereas there was no change in pulse volume of the non-sympathectomized vessels (1.R.T.).

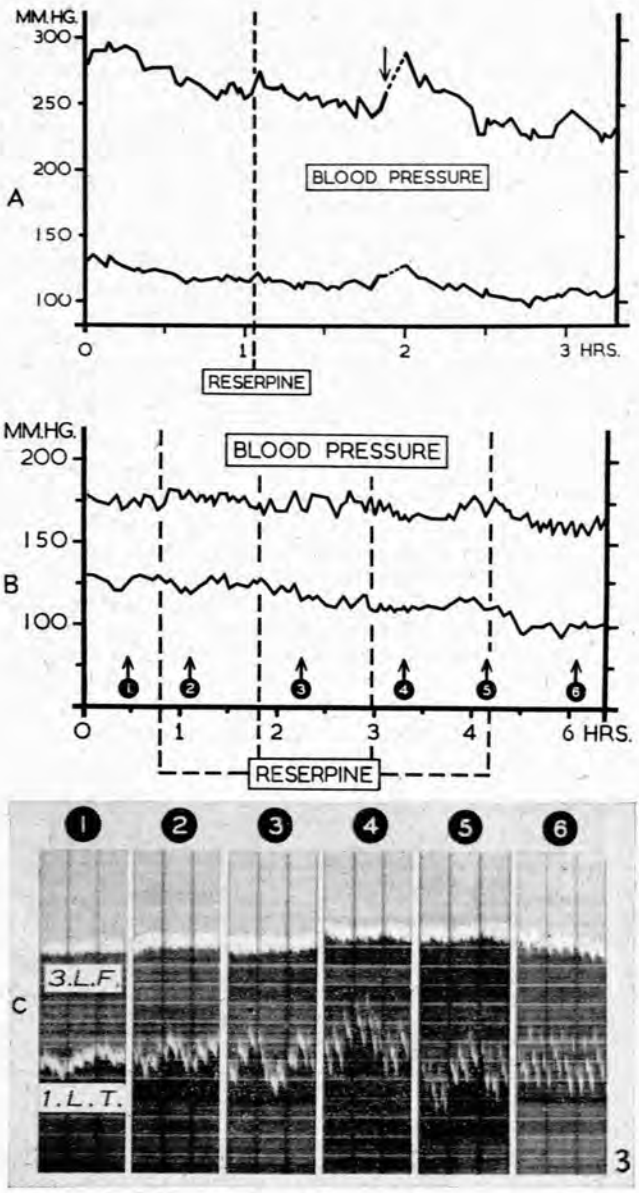

Fig. 3. The effect of intravenous reserpine.
A. In a patient with severe hypertension. Note the rise in blood pressure following the ingestion of a light meal (indicated by the arrow). B. In a patient with mild hypertension. Note the slight fall in blood pressure in A and B as compared with the dramatic response shown in Fig. 4. C. Effect on peripheral blood flow of upper (3.L.F.) and lower (1.L.T.) extremities in a patient whose blood pressure response was seen in Fig. 3B. The tracings of the pulse volume were recorded at the points numbered in the diagram. Note the marked difference in the response between upper and lower extremities. The gradual dilatation obtained in the lower extremities was considered to be the effect of rest rather than that due to the drug.

injection of reserpine produces a marked and relatively rapid vasodilator effect on sympathectomized blood vessels, its effect in the non-sympathectomized extremity is uncertain (Fig. 2) and when vasodilatation takes place it is slow and delayed (Fig. 3C). Lower and upper extremities also seem

to differ in their response inasmuch as vasodilatation is more definite in the upper. This is well illustrated by Fig. 3C and the data were the same in both mild and severe hypertensives.

Towards the end of the test two patients exhibited marked flushing of the face, were sleepy, frequently yawned, and developed conjunctival injection. There was, however, no nasal congestion. Despite the fact that the 'normal' hypertensive patients received large amounts of reserpine the fall in blood pressure was quite unimpressive and was of the same order as might be expected to occur after prolonged rest and mild sedation (Fig. 3A and 3B).

This was in marked contrast to the behaviour of the blood pressure in patients who had undergone Smithwick operations but in whom the hypertension had recurred. Three of the four patients tested received a dose of reserpine that was of the same order as that administered to the 'normal' patients (or slightly smaller). The drop in blood pressure was profound and greatly exceeded that obtained in the latter. Moreover, the fall was rapid and occurred simultaneously with a marked vasodilatation in the sympathectomized lower extremities, usually commencing within 30 minutes of an adequate injection. Fig. 4 illustrates such a case. As the plethysmogram of the normal finger registered spontaneous fluctuations it is to be concluded that such ablation of central vasomotor activity as is said to occur

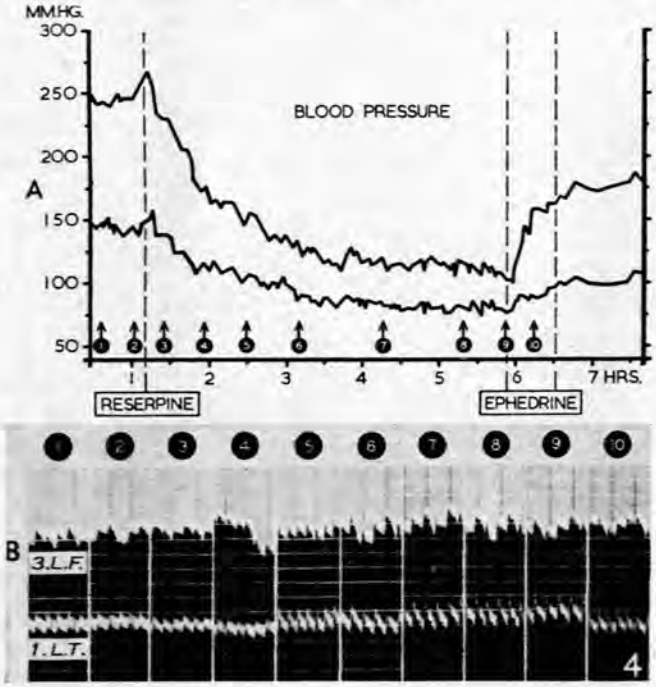

Fig. 4. Effect of 1·5 mg. intravenous reserpine on blood pressure and blood flow of third left finger (3.L.F.) and first left toe (1.L.T.) in a patient who has had a lumbo-dorsal splanchnicectomy (same patient as Fig. 1). Tracing of pulse volume recorded at the points indicated by numbers on the diagram of blood pressure. Note the pronounced fall in blood pressure which was associated with marked vasodilatation in the sympathectomized vessels (1.L.T.). There was some vasodilatation in the non-sympathectomized digit (3.L.F.) as well. To combat fall in blood pressure 1 gr. of ephedrine was given subcutaneously, followed by ½ gr. by mouth.

with reserpine did not entirely abolish reflex vasomotor activity in the peripheral vessels. Being sympathectomized, the vessels of the lower extremities were not affected by this vasomotor activity and, irrespective of the reaction in the upper limb, proceeded to dilate. This lends support to the contention that the dilatation of the sympathectomized vessels in the lower extremities is due to a local effect on the vessel itself.

Pallor of the face was marked in all three cases and shivering, sweating, diarrhoea and angina were also encountered. It was not possible to ascertain whether the pallor was due to active vasoconstriction, occurring in an attempt to maintain the blood pressure, or was due to a postural effect, since all tests were carried out with the patient sitting.

The profound hypotension caused by a single intravenous injection of reserpine in the 'Smithwick' patients responded to subcutaneous injection of ephedrine (Fig. 4). In fact, ephedrine was given in such cases when the drop produced by reserpine caused untoward systemic effects. The hypotension induced by these tests lasted for several hours, and at the next attendance at the hospital a few days later the blood pressure had always risen to almost pre-treatment levels. The degree of hypotension observed in the acute experiment could never be achieved by administering rauwolfia or reserpine by mouth, even if given over a prolonged period.

One of our 'Smithwick' patients responded like the 'normal' hypertensives with a gradual, delayed but marked vasodilatation in both upper and lower limbs and face, unaccompanied by anything but a very minor and insignificant fall in blood pressure. The reason for this different response is not clear; possibly it was related to the fact that the dose of reserpine administered was considerably smaller (1 mg.) than in the other 'Smithwick' patients, who received 1·5-3 mg.

In the patient who had sympathectomies of all 4 limbs, both the upper and the lower extremities responded like the sympathectomized limbs of our 'Smithwick' patients, with a marked and rapid vasodilatation. This was accompanied by marked flushing of the face. However, the fall in blood pressure produced was very slight and was of the same order as that which occurred in the non-sympathectomized patients.

A similar result was obtained in the patient who had had a unilateral lumbar sympathectomy. Marked vasodilatation occurred in the sympathectomized digit, whereas there was no change in pulse volume in the other non-sympathectomized toe (Fig. 2).

This test demonstrated very clearly the uncertainty of the peripheral vascular effect of reserpine on non-sympathectomized vessels. As might be expected in a normotensive patient, the fall in blood pressure was unimpressive.

Discussion

From these results it appears that in man intravenous reserpine has a definite vasodilator effect on sympathectomized blood vessels. This effect must of necessity be a local one on the wall of the vessel itself, unless one postulates stimulation of vasodilator fibres which do not run with the sympathetic, a concept which has not found any acceptance.

This vasodilatation is contrary to observations by McQueen *et al.*[16] to the effect that intraperitoneal reserpine markedly

dilates the non-sympathectomized vessels, but results either in no change or in a decrease in the diameter of the blood vessels of the sympathectomized rabbit's ear. This suggested to McQueen and his colleagues that peripheral vasodilatation is dependent upon the integrity of the peripheral sympathetic nervous system. Quite apart from the fact that it cannot be assumed that results obtained in other species are valid in man, failure of the sympathectomized vessels to dilate might in their experiments have been caused by a shunting of blood into other areas, particularly as a marked general vasodilatation was obtained. Such shunting would have been potentiated if in addition there was a fall in blood pressure, however small.

The vasodilatation obtained in the digital vessels of the 'normal' patients and in the vessels of the upper limbs in some of the 'Smithwick' patients was due to release of central vasomotor tone. Such release is commonly seen on prolonged rest alone, and it cannot with any certainty be ascribed to a central effect of reserpine.

The question of the cause of the pronounced hypotensive effect of reserpine in 'Smithwick' patients is very pertinent. It is generally assumed that the hypotensive effect of reserpine is due to a central inhibition of reflex vasomotor tone. This, however, can no longer be effective in the splanchnicectomized patient and we have to look for a different mechanism. We have shown that in man reserpine has a powerful dilator effect on the sympathectomized vessels of the extremities. There is nothing to militate against the assumption that it has the same action on the sympathectomized splanchnic vessels, which will result in a marked reduction of peripheral resistance and a drop in blood pressure. This concept is supported by the effect of reserpine in the patient who had all four limbs sympathectomized, but whose splanchnic bed was under normal sympathetic control. Marked peripheral vasodilatation was obtained, but was unaccompanied by any significant fall in blood pressure, owing to the fact that the sympathectomized area was small compared with the normal splanchnic bed. It underlines the well-known fact that vasodilatation of the limb vessels alone does not produce a significant drop in blood pressure.

B. CLINICAL ASPECT

Whereas in the experimental field reserpine has been used almost exclusively, all the preparations listed above have been employed in the treatment of hypertension. Although most authors have confined their investigations to one particular rauwolfia preparation, there are some who compared one or more in different groups of patients. Achor *et al.*,[17] for instance, found no difference in the therapeutic action or side-effects between a whole-root preparation and reserpine. Similarly Locket[4] did not detect any difference between a whole-root extract and the alseroxylon fraction, and Moyer *et al.*[18] found that Roxinil had similar actions as the alseroxylon fraction and reserpine. Having compared all the above-mentioned preparations with Rescinnamine, Moyer *et al.*[3] came to the conclusion that there was not much to choose between the five preparations as regards hypotensive effect and the incidence of side-effects. The severity, however, of side-effects, including depressive reactions, was most marked in the patients treated with reserpine.

Side-effects and toxic reactions of reserpine have received the greatest publicity, but whether this is due to the large number of patients treated with this preparation, or whether it is a true index of greater toxicity as Moyer *et al.*[3] suggest, remains to be confirmed.

That *Rauwolfia serpentina* is not the whole answer to the treatment of hypertension has been abundantly demonstrated by the number of authors who have been forced to combine it with other drugs. The combination most widely used and generally accepted as the best treatment for severe hypertension, is pentapyrrolidinium and a rauwolfia preparation, usually reserpine.[19-21] This combination has proved more potent than either drug alone, thus causing fewer side-effects. Moreover, a more sustained hypotensive effect is obtained than if pentapyrrolidinium is used alone. The results have been more controversial when *Veratrum viride* or hydralizine was combined with rauwolfia.

Whereas there seems little to choose between the various rauwolfia preparations, the question which type of patient will respond best to treatment, and the degree of hypotension to be expected in the individual patient, is more difficult to answer. In our clinic we see a large number of patients with arteriosclerosis complicated by hypertension where treatment presents a special problem owing to complications such as cerebro-vascular accidents, and in whom the indications for hypotensive drugs are by no means unquestioned. We also see cases who have been treated in the past by lumbo-dorsal splanchnicectomy and in whom hypertension has recurred. Little has been found in the literature about the use of hypotensive drugs in the latter group. It is also by no means settled whether the response is different in mild, as opposed to severe, cases of hypertension. We have therefore instituted investigations into these two groups of patients, viz. (*a*) patients with long-standing hypertension associated with advanced arteriosclerosis affecting coronary, renal, cerebral and peripheral vessels, who had responded poorly to treatment in the past, and (*b*) cases whose hypertension recurred after lumbo-dorsal sympathectomy. The average blood pressure of group (*b*) before treatment was 238/141 mm. Hg. Only one of all the patients had normal fundi and all but one had evidence of left ventricular hypertrophy.

All patients were seen by special appointment first at weekly intervals, and later fortnightly. Blood-pressure readings were taken after a period of rest of 15-20 minutes. Some of the hypotensive drugs produce postural hypotension and the position of the patient at the time of reading the blood pressure was important. In fact, pressure readings with the patient lying down may bear very little resemblance to the pressure in the ambulant patient and may be very misleading as regards the efficacy of the treatment under review. We therefore measured the blood pressure at half-minute intervals first in the recumbent and then in the erect posture. A minimum of 6 readings and a maximum of 10 were taken in each position. From these figures an average blood-pressure reading for both positions was obtained at every attendance. The pulse rate was taken at the end of each series of blood-pressure recordings.

Before treatment was begun, a full investigation of each patient was made, including a detailed history, physical examination, examination of fundi, urinalysis, blood urea, electrocardiogram, X-ray of chest, phenolsulphonphthalein (PSP) excretion test. Patients were seen on several occasions before the commencement of treatment.

The patients were first given Rauwiloid and, according to the effect on the blood pressure, Veriloid* was subsequently added. The dosage of this was cautiously increased until either a satisfactory hypotensive effect was obtained or nausea and vomiting precluded a further increase in dosage. If the reduction was still unsatisfactory, pentolinium was added.

For the purpose of evaluating the results, the following scheme of grading was adopted. Irrespective of the height of the initial blood pressure a fall of 30 mm. Hg in systolic blood pressure, in either the lying posture or the standing, was considered a 'good' response. A fall in blood pressure between 20 and 30 mm. Hg was charted as 'moderate' and smaller changes as 'no' response.

(a) Effect on Blood Pressure

Of the 20 patients treated with Rauwiloid, 6 responded inadequately within 6-12 weeks' treatment and it was felt

TABLE II. BLOOD-PRESSURE RESPONSE IN PATIENTS WITH RAUWILOID OR RAUWILOID + VERILOID

Drug Used	*No. of Patients*	*Good Response (Fall over 30 mm. Hg)*		*Moderate Response (Fall over 20 mm. Hg)*		*No Response (Fall under 20 mm. Hg)*	
		No.	*%*	*No.*	*%*	*No.*	*%*
Rauwiloid	20	9	45	5	25	6	30
Rauwiloid or Rauwiloid + Veriloid ..	22	10	45	5	23	7	32

unjustifiable to withhold other drugs, which were accordingly added. The rest of the patients were treated from 4-6 months.

Of the 20 patients who received Rauwiloid only, 9 (45%) showed a good response, the average fall in blood pressure being 38 mm. Hg in the lying position and 36 mm. Hg in the standing. The response was moderate in 5 (25%), the average fall being 21·4 mm. Hg in the lying position and 20·8 in the standing. Rauwiloid had no effect in 6 patients (30%)—Table II.

Because there had been little or no response to treatment with Rauwiloid alone, or because a further fall in blood pressure seemed desirable, 6 patients were in addition treated with Veriloid. In only one did the addition of Veriloid lower the blood pressure sufficiently to upgrade this patient from the 'moderate' into the 'good' response group, and those patients who had not responded to treatment with Rauwiloid alone also did not respond after Veriloid had been added. In fact, the average fall in blood pressure after treatment with Rauwiloid was practically identical with that obtained after additional treatment with Veriloid or after treatment with Rauwiloid and Veriloid from the start.

We therefore concluded that there was very little to be gained by the additional administration of Veriloid to patients who were already treated with Rauwiloid. Moreover, Veriloid produced vomiting in most patients at one stage or another during treatment and the dosage had to be adjusted accordingly. In 3 patients vomiting proved troublesome and necessitated the cessation of treatment.

(b) Height of the Initial Blood Pressure in Relation to the Therapeutic Response

The question arose whether the height of the blood pressure had any relation to the response to be expected. It was found that the patients who responded best had an average blood pressure of 203/117 mm. Hg, those who responded moderately well a blood pressure of 214/131 mm. Hg, and those who did not respond at all the highest average pressures, namely 223/133 mm. Hg (Table III). Our results, therefore, agree with other authors, who found that a larger percentage of patients with mild hypertension responded to treatment and that a higher percentage of failures is seen in the more severe type.

TABLE III. INITIAL BLOOD PRESSURE IN RELATION TO THERAPEUTIC RESPONSE IN 22 PATIENTS TREATED WITH RAUWILOID OR RAUWILOID + VERILOID

B.P. Response	*No. of Patients*	*Percentage of Total*	*Initial B.P.*
Fall of over 30 mm. Hg	10	45	203/117
Fall of over 20 mm. Hg	5	23	214/131
Fall of under 20 mm. Hg	7	32	223/133

Whereas this holds good for groups of patients, in the individual patient the result cannot be predicted. This is very clearly demonstrated if all the patients are divided into two groups, viz. (*a*) those with an initial diastolic blood pressure above 120 mm. Hg, and (*b*) those with an initial diastolic blood pressure below 120 mm. Hg. In Table IV it will be seen that of the patients with the higher diastolic pressures 25% responded well (fall in diastolic blood pressure of more than 30 mm. Hg) and 42% failed to respond, as against 70% and 20% respectively in those patients whose diastolic blood pressure was below 120 mm. Hg. The average fall in blood pressure of the severe hypertensive who reacted was, however, much greater than in the milder cases; that is to say, if a severe hypertensive does respond well to Rauwiloid the actual fall in blood pressure will easily exceed anything seen in the moderate group. It is because of this excellent response in the few cases with severe hypertension that the average fall in blood pressure in the severe group as a whole is slightly better than the average fall in blood pressure of the mild group. It would thus be misleading to consider only the averages. It will also be seen from Table IV that a relatively large percentage of patients with an initial diastolic pressure of above 120 mm. Hg exhibited moderate response. However, it must be realized that a fall in blood pressure of 20-30 mm. Hg systolic in a patient with severe hypertension constitutes a poor therapeutic response, whereas an equivalent fall in mild hypertension represents a satisfactory therapeutic result.

TABLE IV. THERAPEUTIC RESPONSE ACCORDING TO INITIAL DIASTOLIC BLOOD PRESSURE PATIENTS TREATED WITH RAUWILOID OR RAUWILOID + VERILOID

Therapeutic Response	*Initial Diastolic B.P. above 120 mm. Hg*			*Initial Diastolic B.P. below 120 mm. Hg*		
	No.	*%*	*Av. fall B.P.*	*No.*	*%*	*Av. fall B.P.*
Good	3	25	42/30	7	70	34/17
Moderate	4	33	21/13	1	10	21/18
Nil	5	42	5/10	2	20	8/10
Total	12	100	23/15	10	100	12/12

(c) Results in Hypertensive Patients who have undergone a Lumbo-Dorsal Splanchnicectomy (Smithwick operation)

In view of the fact that a marked fall in blood pressure could be produced in this group of patients by the intravenous injection of reserpine in the acute experiments, the results of long-term oral therapy with Rauwiloid tablets were of

* A compound tablet consisting of 1 mg. of Rauwiloid and 3 mg. of *Veratrum viride*.

TABLE V. COMPARISON OF RESULTS IN PATIENTS WHO HAVE AND WHO HAVE NOT HAD A PREVIOUS SMITHWICK OPERATION

	'Smithwick' Patients	'Non-Smithwick' Patients
No. of patients	8	14
Initial B.P.	238/141*	198/116*
	218/135†	193/118†
Fall of over 30 mm. Hg	2 (25%)	8 (57%)
Fall of over 20 mm. Hg	2 (25%)	3 (21·5%)
Fall of under 20 mm. Hg	4 (50%)	3 (21·5%)

* Lying. † Standing.

considerable interest. The fact that the therapeutic response in these patients was much worse than in the 'normal' patients came as a surprise. In Table V it will be seen that of the 'Smithwick' patients only 2 (25%) responded well, 2 (25%) moderately, and 4 (50%) not at all.

It must be pointed out that the average blood pressure in the 'Smithwick' patients before treatment was 238/141 mm. Hg lying and 218/135 standing, whereas in the 'non-Smithwick' group the blood pressure was 198/116 lying and 193/118 standing. In the light of what has been said above, the response is probably a reflection of the difference in the initial height of the blood pressure in the two groups.

(d) Effect of Reserpine

Since it has been claimed that reserpine, has a greater therapeutic effect than other rauwolfia preparations, the effect of the pure alkaloid (Serpasil, 1·25 mg. per day) was tried on 7 patients to see whether a further fall in blood pressure could be produced.

There was no essential difference in the recumbent blood pressure in any of the patients when reserpine was added, irrespective of whether they had been treated with Rauwiloid, or with a combination of Rauwiloid and Veriloid and Ansolysen. In 2 patients, however, there was a slight fall in the standing blood pressure. In contrast to the doubtful therapeutic response, we encountered one definite toxic reaction in a patient who had tolerated 4 mg. of Rauwiloid per day for 1 year, without any trouble. After only 1 week of treatment he developed nervousness, insomnia and depression with brooding thoughts and fear of impending death.

We, therefore, felt that not only was there no additional advantage in giving reserpine, but that it produced nervousness and depression which had been absent even on prolonged treatment with Rauwiloid.

(e) Effect on Symptoms other than Blood Pressure

Angina. A most gratifying result was obtained in 4 patients who had angina before treatment commenced. There was marked improvement in 2 and some improvement in the other 2 patients. One patient, who had been practically incapacitated by very frequent attacks of angina and a severe shoulder-hand syndrome, on treatment with Rauwiloid experienced marked relief, the frequency of attacks decreasing from about 15 to 1 or 2 per day. At the same time physiotherapy became more effective and resulted in almost complete relief of her shoulder-hand syndrome. In another patient the frequency of the attacks was reduced from 3-4 per day to 2-3 per week. In the other 2 patients, who had less frequent attacks of angina before commencing treatment, there was a definite improvement both in the severity and number of attacks, but not complete relief.

Intermittent Claudication. Six patients complained of intermittent claudication. There was very slight improvement in 3 and none in the other 3.

Postural Hypotension. This was an interesting side-effect noted in 3 'Smithwick' patients, who had had this symptom in a mild degree before the commencement of therapy. Only one of these belonged to the 'good response' group and in her the hypotension was so marked that she fainted one morning. The other two had only responded with a moderate fall in blood pressure and it is of interest to note that a relatively small drop in blood pressure produced a marked increase in postural hypotensive symptoms.

Complications. Congestion of the air passages and sleepiness were mentioned by one or two patients, but never proved troublesome symptoms.

Myocardial Infarction. Two patients developed myocardial infarction while under treatment. One of these had had 2 attacks of angina at rest before the commencement of treatment. In his case the infarction occurred after an episode of severe vomiting induced by Veriloid, and the resultant dehydration might well have been a predisposing factor in the production of a coronary thrombosis. The blood-pressure readings a few days before the infarction had not been particularly low. The other patient had a typical history of a previous infarction 8 years before, but without any residual changes in the electrocardiogram. A third patient developed an extension of an old posterior myocardial infarction. In both these latter cases the exact time of the infarction is not known, and there had been no episodes of marked hypotension. This relatively high incidence of cardiac complications is a reflection of the type of case treated rather than the result of therapy.

Mental Depression. This has been mentioned frequently in the literature as one of the serious side-effects of Rauwolfia therapy. In our series mental depression, bordering on mild psychosis, was recorded in only one patient, who had been treated with Rauwiloid for 5 months, the dose during the last 2 months having been increased from 8 mg. per day to 12 mg. per day. This man became extremely nervous, restless, anxious and somewhat agitated and also developed attacks of 'shakiness and tremors', which cleared up 2-3 weeks after Rauwiloid was withdrawn. In 3 other patients attacks were encountered which were variously described as 'shaking' or 'shivering', and were frequently associated with a feeling of nervousness and unrest. In every case the attacks ceased after Rauwiloid was stopped or the dose reduced. All but one of these 4 patients had been on large doses of Rauwiloid (12 mg. per day) for some considerable time, and 3 of them were extremely nervous and apprehensive individuals. One other patient was unusually sensitive to the drug. She developed insomnia, nervousness, tremor, arthralgia and joint stiffness, necessitating withdrawal of the drug after only 2 weeks' treatment.

DISCUSSION

Whereas there is considerable divergence in opinion on the results of treatment of mild hypertension with Rauwolfia alkaloids, the percentage response reported varying from 25%[19] to 100%[22] in different series, it would appear from the literature that patients with fixed hypertension and arteriosclerosis respond less well to hypotensive drugs than those with the early and labile type.[23,24] Our results are

quite compatible with this view. Examining a series of long-standing cases of hypertension with marked arteriosclerosis, we obtained a good response in 45% of cases, a moderate response in 23% and no response in 32%.

It has been stated that severe cases with symptoms frequently respond better than milder cases.[4] We agree with that view only in so far that if a patient with severe hypertension responds to treatment the fall in blood pressure is commonly greater than the drop obtained in a patient with mild hypertension. In our group of patients the percentage of good responses was much greater in the mild cases than in the severe ones. This was brought out very clearly when we divided our cases into those with diastolic pressures above and below 120 mm. Hg. Only 25% of the former showed a good response as opposed to 70% of the latter. In this our results differ from those of McGregor and Segel[25] and Moyer,[26] who found Rauwolfia equally effective in both mild and severe cases, and from those of Platt and Sears[27] who obtained a 'significant and sometimes profound effect in at least 40% of cases' all of whom had severe hypertension.

Although in the acute experiment an excellent hypotensive effect was obtained with reserpine in 'Smithwick' patients, on prolonged oral therapy these patients behaved in exactly the same way as all other patients with severe hypertension.

Our patients who had been on an adequate dose of Rauwiloid have not derived any benefit when Veriloid or Serpasil were added in an attempt to obtain a further fall in blood pressure. The results obtained with Rauwiloid alone were the same as with any other combination administered in these investigations. The difficulties and complications encountered in the administration of Veriloid far outweighed its therapeutic value. It must be admitted, however, that all our patients had been treated first with Rauwiloid and that the results may have been different had treatment been commenced with veratrum and Rauwiloid added subsequently.

Severe mental depression occurred in only one of our patients, but 3 others complained of nervousness, shakiness and unrest and one of these also developed arthralgia.

Unlike Smirk and McQueen's patients,[28] who were treated with reserpine, none of our patients needed psychiatric treatment and all toxic symptoms spontaneously cleared up after cessation of therapy. We also have evidence in one case that reserpine is more toxic than the alseroxylon fraction —a similar observation to that previously reported on the comparison of reserpine and rescinnamine.[28]

We would agree that with a higher dosage of Rauwiloid toxic reactions are more liable to occur.[4] However, 2 of our patients developed nervousness, tremor and anxiety when on only 4 mg. of Rauwiloid per day.

The alseroxylon fraction is, therefore, by no means without its unpleasant side-effects, although they are probably less severe than those encountered with reserpine.

SUMMARY AND CONCLUSION

The effect of intravenous reserpine on peripheral blood flow and blood pressure was investigated in a group of 'normal' hypertensive patients and compared with a group of hypertensives who had previously undergone a lumbo-dorsal splanchnicectomy.

It was shown that the hypotensive effect was much larger in the latter group, and this was thought to be related to the marked vasodilator action which intravenous reserpine has on sympathectomized blood vessels.

Vasodilatation was only associated with a dramatic fall in blood pressure if the sympathectomized vascular bed was large enough, i.e. if the splanchnic bed was sympathectomized as well. The hypotensive effect was transient, and comparable low blood-pressure levels could not be maintained by oral administration in the same 'Smithwick' patients.

The effect of reserpine on the non-sympathectomized vessels was unpredictable and did not bear any constant relation to the moderate drop in blood pressure obtained.

On long-term treatment with Rauwiloid there was no difference in the therapeutic response between the 'normal' and the sympathectomized hypertensive patients, and Rauwiloid was found useful in 45% of cases.

We could arrive at no conclusion as to which case would respond best to treatment although, as might be expected, a bigger fall in blood pressure was obtained in patients with a more severe hypertension but a larger percentage of the milder cases responded to treatment.

Rauwiloid produced unpleasant side-effects in 22% of cases.

In our series the addition of Veriloid was of very little benefit and certainly did not justify the amount of time and trouble spent in stabilization both for the patient and the physician.

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